Remarks/Arguments

The foregoing amendments to the claims are of formal nature, and do not add new matter. Claims 119-126 and 129-131 were pending in this application and were rejected on various grounds. As explained below, Applicants rely on assay 94: Detection of polypeptides that affect glucose or FFA uptake by primary rat adipocytes (or 'the glucose/FFA uptake assay,' see Example 158, page 530 of the specification) for patentable utility of PRO1182 and its antibodies. Therefore, Claims 119-123 have been amended to remove references to the "gene amplification assay" and instead now, recite the functional recitation: "wherein said polypeptide inhibits the uptake of glucose or FFA (free fatty acids) by adipocyte cells."

Errors within the response of March 10, 2005 remarked by the Examiner have been presently amended; however since the Examiner indicated that the previous amendment was not fully responsive, Applicants assume that the amendment filed March 10, 2005 was not entered. Therefore, Applicants retain the marked-up version of the previously amended claims for clarity and request that the present amendments be considered and entered for the record and that the response of March 10, 2005 be disregarded.

The previous rejections are discussed in view of the present claim amendments.

Continuity

Applicants have amended the pending claims to remove references to the "gene amplification assay." Applicants rely on assay 94: Detection of polypeptides that affect glucose or FFA uptake by primary rat adipocytes (or 'the glucose/FFA uptake assay,' see Example 158, page 530 of the specification) for patentable utility of PRO1182 and its antibodies. This assay was first disclosed in International Application PCT/US00/08439, filed March 30, 2000, priority to which has been claimed in this application. As discussed below, the glucose/FFA uptake assay of the instant application, was a "well-established assay" that was well-known around the effective filing date of March 30, 2000. Hence, Applicants believe that they are entitled to at least an effective filing date of **March 30, 2000** for this application.

Claim Rejections – 35 USC § 101 and 112, first paragraph

Claims 119-131 are rejected under 35 U.S.C. §101 allegedly "because the claimed invention lacks a credible, specific and substantial asserted utility or a well established utility."

Claims 119-131 are further rejected under 35 U.S.C. §112, first paragraph allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention".

As discussed above, Applicants rely on assay 94: 'the glucose/FFA uptake assay,' for patentable utility of the PRO1182 polypeptide and submit that the specification provides sufficient disclosure to establish a specific, substantial and credible utility for the PRO1182 polypeptide at least in Example 158, page 530 of the specification. The adipocyte glucose/FFA assay of the instant application is performed as follows: primary rat adipocyte cells are plated on a 96 well plate and incubated overnight with media supplemented with PRO1182 polypeptide. After the initial overnight incubation, samples of the media are taken at hour 4 and hour 16 and residual glycerol, glucose and FFA are measured. After the hour 16 sample is taken, insulin is added to the media and the adipocytes are allowed to incubate for an additional 4 hours. After this final 4 hour incubation, another sample is taken and residual glycerol, glucose and FFA is measured again. As a control, identical incubations and samplings are performed on cells that have been incubated overnight in media initially supplemented with insulin rather than PRO1182 polypeptide. Results are scored as positive in the assay if the uptake is greater than 1.5 times (stimulatory) or less than 0.5 time (inhibitory) the uptake of the insulin control. As PRO1182 resulted in less than 0.5 the uptake of the insulin control, PRO1182 tested positive as an inhibitor of glucose/FFA uptake in adipocyte cells.

The adipocyte glucose/FFA uptake assay was designed to determine whether a polypeptide is capable of modulating, either positively or negatively, the uptake of glucose, or free fatty acids by adipocyte cells. The assay identifies polypeptides that are useful for treating disorders wherein stimulation or inhibition of glucose uptake by adipocytes is therapeutically effective. That is, a protein or agent which directly or indirectly increases glucose transport in this assay is potentially useful in the treatment of metabolic disorders as discussed herein. Therefore, one skilled in the art would readily understand that a protein that inhibits glucose

uptake into adipocytes is a therapeutic target, since blocking its function would 'decrease' the inhibition, and thus, increase glucose uptake into adipocytes. Examples of such metabolic disorders where such polypeptides or agents are useful include, but are not limited to, obesity, diabetes, and hyper- or hypo-insulinemia. Therefore, the skilled artisan would readily recognize a utility for PRO1182 polypeptide based on its positive hit in the adipocyte glucose/FFA uptake assay.

Applicants further submit that the glucose/FFA uptake assay, as described in Example 158 of the instant application, was a "well-established assay" around the effective filing date of March 30, 2000. In fact, the art available around the effective filing date of March 30, 2000, strongly provided the necessary nexus between proteins that test positive in the adipocyte glucose/FFA assay and metabolic disease treatment. For example, it was well known in the art well before March 30, 2000 that increased glucose uptake by adipocyte cells was the hallmark of a number of therapeutically effective agents, such as troglitazone and poiglitazone. (Tafuri, *Endocrinology*, 137(11): 4706-4712 (1996); Sandouk, *et al., Endocrinology*, 133(1):352-359 (1993) - copy enclosed with previously submitted IDS). Both troglitazone and poiglitazone are members of the thiazolidinedione class of compounds and have been used to effectively treat noninusulin-dependent diabetes mellitus (NIDDM), the most common form of diabetes. Both compounds were shown to function, at least in part, by increasing the number of cellular glucose transporters in order to facilitate increased glucose uptake.

It had also been shown that 'vanadium salts' could be a potential treatment for diabetes and several clinical trials had already been performed as of the effective filing date of March 30, 2000 (see page 26617, right column, Goldwaser *et al.*, *J. Biol Chem.*, 274(37):26617-26624 (1999) - copy enclosed with previously submitted IDS). Using a rat adipocyte culture system, similar to the system disclosed in the instant application, Goldwaser *et al.* showed that vanadium ligand l-Glu (γ)HXM potentiates the capacity of free vanadium ions to activate glucose uptake and glucose metabolism in rat adipocytes *in vitro* by 4-5 folds and to lower blood glucose levels in hyperglycemic rats *in vivo* by 5-7 folds. Similar assays were commonly used to identify potential anti-diabetic agents and to examine the regulatory mechanisms of important molecules involved in fat cell metabolism.

In another study, Mueller *et al.*, who were interested in determining the influence of glucose uptake on leptin secretion, employed essentially the same assay to measure changes in glucose uptake after insulin exposure. (Mueller *et al., Endocrinology*, 139(2): 551-558 (1998) - copy enclosed with previously submitted IDS). Figure 1A showed the glucose concentrations in medium from 0-96 hours from isolated rat adipocytes in primary culture with various insulin concentrations. As indicated by the decrease in glucose in the medium in the Figure, Mueller *et al.* suggested that insulin produced a concentration-dependent increase in glucose uptake by the cultured adipocytes. Based on these experimental results, the authors stated that insulin increased leptin secretion over 96 hours, and that the increase in leptin was more closely related to the amount of glucose taken up by the adipocytes than to the insulin concentration, suggesting a role for glucose transport and/or metabolism in regulating leptin secretion. (See Abstract).

Using the same assay system, Mueller *et al.* further studied the effect of two well-known anti-diabetic agents, metformin and vanadium, on leptin secretion. These agents were known to enhance glucose uptake. (Muller *et al.*, *Obesity Research,* 8(7): 530-539 (2000) - copy enclosed with previously submitted IDS). Mueller's experimental data indicated that both metformin and vanadium increased glucose uptake and inhibited leptin secretion from cultured adipocytes. Further, as was well known in the art at the time of the instant filing, leptin was involved in the regulation of food intake, energy expenditure and body fat stores (that is, the metabolic status of an organism). As disclosed by Mueller *et al.* (1998) on page 551, column 1, leptin was known to decrease after fasting or caloric restriction and increase several hours after refeeding. Based on Mueller's teachings, it was known that "agents modulating leptin regulation" would be useful in treating obesity. Thus, taken together along similar lines, one skilled in the art would have known that an inhibitor of adipocyte glucose uptake like PRO1182 would be useful to investigate leptin regulation, and potentially, for obesity treatment.

These studies discussed above clearly established the usefulness of agents identified through the glucose/FFA uptake assay as therapeutic agents for treating metabolic diseases such as obesity, diabetes, hyper- or hypo-insulinemia. In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions that **Office personnel must be careful not to interpret the phrase "immediate benefit to the public"** or similar formulations used in certain court decisions **to mean that products or services based on the claimed invention must be "currently**

available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a '"substantial" utility'"[1] (emphasis added). Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement states, "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility." Accordingly, Applicants respectfully submit that Applicants' assertion that the claimed PRO1182 proteins have utility in the field of treatment of metabolic diseases such as diabetes, obesity, etc. is substantial.[1]

In view of the above, Applicants respectfully submit that the specification discloses at least one credible, substantial and specific asserted utility for the polypeptide PRO1182. Further, based on this utility, the disclosure in the specification, the well-established knowledge in the art (at the effective date of filing) regarding agents that modulate or regulate glucose uptake and their usefulness in treatment of metabolic diseases, one skilled in the art would have known how to use the claimed PRO195 polypeptide. Accordingly, the Examiner is requested to reconsider and withdraw the present rejection under 35 U.S.C. §101 and §112, first paragraph.

Claim Rejections – 35 USC § 112, first paragraph- Written Description

Claims 119-131 are also rejected under 35 U.S.C. 112, first paragraph because, according to the Examiner, the subject matter was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time of filing." Further, the Examiner contends that "the specification teaches a polypeptide (SEQ ID NO: 357) but does not teach functional or structural characteristics of all claimed polypeptides. The description of one PRO polypeptide (SEQ ID NO: 357) is not adequate written description of an entire genus of functionally equivalent polypeptides." Applicants respectfully traverse this rejection.

---

[1] *Id.* at 534, 148 U.S.P.Q. (BNA) at 695.

The Legal Test for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph is "whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language."[2, 3] The adequacy[4] The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. [5, 6]

In *Environmental Designs, Ltd. v. Union Oil Co.*,[7] , the Federal Circuit held, "Factors that may be considered in determining level of ordinary skill in the art include (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field." [8] Further, the hypothetical 'person having ordinary skill in the art' to which the claimed subject matter pertains would, of necessity, have the capability of understanding the scientific and engineering principles applicable to the pertinent art" (Emphasis added).[9, 10]

---

2 *In re Kaslow*, 707 F.2d 1366, 1374, 212 USPQ 1089, 1096 (Fed. Cir. 1983).

3 *see also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991).

4 *See, e.g., Vas-Cath*, 935 F.2d at 1563; 19 USPQ2d at 1116.

5 *Union Oil v. Atlantic Richfield Co.*, 208 F.2d 989, 996 (Fed. Cir. 2000).

6 *See also* MPEP §2163 II(A).

7 713 F.2d 693, 696, 218 USPQ 865, 868 (Fed. Cir. 1983), *cert. denied*, 464 U.S. 1043 (1984).

8 *See also* MPEP §2141.03.

9 *Ex parte Hiyamizu*, 10 USPQ2d 1393, 1394 (Bd. Pat. App. & Inter. 1988).

10 *See also* MPEP §2141.03.

The specification provides sufficient written description for the claimed invention:

Whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains.

Applicants respectfully submit that the instant invention evidences the actual reduction to practice of a full-length PRO1182 of SEQ ID NO: 357, with or without its signal sequence, or encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203088. Further the amended claims recite the functional recitation: "wherein said polypeptide inhibits the uptake of glucose or FFA (free fatty acids) by adipocyte cells," which, as discussed above, is based on a well-established assay known to the skilled artisan at the effective filing date of this application. Therefore, the polypeptides are defined both by functional as well as structural features. As stated above, the Examiner acknowledged that the sequence set forth in SEQ ID NO: 357 meets the written description provision of 35 U.S.C. §112, first paragraph. Thus, genus polypeptides with at least 80% sequence identity to SEQ ID NO: 357, wherein the polypeptide possesses the functional property of inhibiting the uptake of glucose or FFA by adipocyte cells would meet the requirement of 35 U.S.C. §112, first paragraph, as providing adequate written description.

The instant specification provides methods for determining percent identity between two amino acid sequences. In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. The specification describes methods wherein the polypeptides with at least 80% identity to SEQ ID NO:357 inhibit the uptake of glucose or FFA by adipocyte cells. From the specific activity of the claimed polypeptide, the description of the claimed genus is achieved. Hence, Applicants respectfully request that this rejection be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-2730P1C33). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: June 23, 2005

Daphne Reddy

Daphne Reddy
Reg. No. 53,507

HELLER EHRMAN, LLP
Customer No. 35489
275 Middlefield Road
Menlo Park, California 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

SV 2131717 v1
6/23/05 12:07 PM (39780.2730)